Remarks

Claims 1-9 and 17-21 will be pending in the application upon entry of the present amendment. Claims 10-15, previously withdrawn, are now canceled. Claims 1 and 17 are currently amended. Claim 16 is canceled.

Claims 1-9 and 16-21 stand rejected. Reconsideration is respectfully requested in view of the present claim amendments and following remarks.

Support For Claim Amendments

Claim 1 has been amended to recite that the at least one compound according to Formula I is an (*R*)-enantiomer substantially free of its corresponding (*S*)-enantiomer, with respect to the absolute configuration at the 5-position of the benzodiazepine ring. This amendment finds support in original claim 16 (now canceled) as well as in the specification at page 39, lines 4-6.

Claim 17 has been amended to depend from claim 1.

Claim 21 has been amended to remove a limitation that is redundant. The limitation is already contained in the ultimate base claim, claim 1.

Response to 35 U.S.C. §103(a) Rejection

The Examiner has rejected claims 1-9 and 16-21 under 35 U.S.C. §103(a) over Ito, *et al.*, "Pharmacological studies of Tofisopam," *Res. Lab Pharamacol.*, Vol. 12, No. 2 (1981), (hereafter "Ito") in view of U.S. Patent No. 6,093,740, to Jirousek, *et al*, ("Jirousek").

According to the Examiner, Ito discloses the pharmacological effects of tofisopam, both *in vivo* and *in vitro*. In particular, the Examiner notes that Ito teaches that tofisopam increases an animal's pain threshold when given in excess of 1000 mg/kg. The Examiner further states that Ito discloses the utility of tofisopam for treatment of edema formation, noting that oral administration of 160 mg/kg suppresses spontaneous locomotion and that administration of more than 300 mg/kg inhibits acetic acid induced stretching. In addition to the above, citing paragraphs 3 and 4 of Ito, the Examiner states that Ito discloses that the intravenenous administration of 3 mg/kg of tofisopam has 1) a hypotensive effect, relaxing the action of smooth

muscular organs; and 2) an antagonistic action to acetylcholine, histamine, barium chloride, and nicotine.

Following the discussion of Ito, the Examiner discusses Jirousek, which the Examiner states is directed to the treatment of dermal edema. The Examiner then concludes that a person of ordinary skill in the art would have been motivated to modify Ito in view of Jirousek to arrive at the presently claimed method. According to the Examiner, this motivation would have derived from Ito and Jirousek's discussion of inflammatory disorders. The Applicants respectfully disagree.

A person of ordinary skill in the art would not have combined Ito and Jirousek as these references have nothing in common to provide a motivation for their combination. In particular, and not withstanding the Examiner's statement to the contrary, Ito is ***not*** directed to the treatment of an inflammatory disorder using tofisopam. Rather, Ito provides a summary of the *in vivo* and *in vitro* activities of tofisopam, none of which relate to inflammatory disorders.

Moreover, Ito does not disclose the administration of tofisopam as a treatment of edema formation. Rather, Ito states unequivocally that tofisopam had ***no effect*** on paw edema formation. See paragraph 5, page 588 of Ito which states that "[t]he effects of [tofisopam] on the erythrocyte membrane, paw edema formation, vascular permeability, blood sugar level, and coagulation system **were not found**." (emphasis added). Thus, Ito's paragraph 5 provides no support for the Examiner's contention that Ito is directed to treatment of an inflammatory disorder.

The Applicants further submit that the Examiner's reliance on paragraphs 1 through 4 of Ito for the purpose of establishing that tofisopam has anti-inflammatory properties is equally flawed.

According to paragraph 1, pg. 587 of Ito's "summary," administration of tofisopam results in behavioral and physiological changes similar to those observed upon administration of diazepam. According to Ito, however, tofisopam must be dosed at substantially higher levels to achieve diazepam-like results. In order to illustrate the efficacy differences between diazepam and tofisopam, Ito reports that spontaneous locomotion in rats, *i.e.* the ability to walk, was lost at

a dose of just 4.2 mg/kg for diazepam, but required a dose of 160 mg/kg of tofisopam. This is nearly a 40 fold difference.

Paragraph 1 further states that tofisopam doses of over 300 mg/kg significantly inhibit acetic acid-induced stretching. The acetic acid-induced stretching model is well known in the art as a measure of the ***analgesic*** properties of a given molecule. The acetic acid-induced stretching model does not, however, teach or otherwise suggest whether a given molecule has any ability to reduce inflammation. What is more, the Examiner has failed to provide any evidence that the reduction in stretching correlates to an anti-inflammatory property of tofisopam.

Finally, paragraph 1 states that mice dosed with tofisopam at greater than 1,000 mg/kg display a higher than average pain threshold. This finding appears to be consistent with the ability of tofisopam to reduce acetic acid-induced stretching. It does not, however, indicate the mechanism by which the animals' pain threshold is increased. As a result, a person of ordinary skill in the art would not understand Ito's disclosure of an increased pain threshold to denote anti-inflammatory activity. And, as with the acetic acid-induced stretching model, the Examiner has not identified any facts correlating the increase in pain threshold with the anti-inflammatory properties of tofisopam.

Thus, none of the discussion in Ito's paragraph 1 teaches, discloses, or otherwise suggests the utility of tofisopam for reducing inflammation or treating an inflammatory disorder.

Paragraph 2 in Ito's summary is directed to the hypotensive effect of tofisopam. As is widely understood in the art, "hypotension" refers to low blood pressure. Thus, a person of ordinary skill in the art understands that dosing a rabbit with 3 mg/kg of tofisopam results in a blood pressure decrease. Paragraph 2 then details the further effects of this dose of tofisopam. These further effects include blood vessel dilation, relaxation of isolated rabbit aortas and pig coronary arteries, and the inhibition of adrenaline-induced arrhythmia and vasopressin induced angina pectoris. None of the above described actions of tofisopam, however, teach or suggest that tofisopam has anti-inflammatory activity. And, once again, the Examiner has provided no link between the disclosed activities and anti-inflammatory activity.

Paragraph 3 of Ito is directed to tofisopam's activity as a smooth muscle relaxant and its utility as an antagonist to acetylcholine, histamine, barium chloride, and nicotine. Paragraph 3

further discusses the utility of tofisopam in reducing small intestine propulsion. Here again, however, none of the activities disclosed in paragraph 3 teach, suggest, or otherwise disclose the utility of tofisopam for the treatment of inflammation. And, as with paragraphs 1 and 2, the Examiner has failed to establish a link between the activities described in paragraph 3 and the treatment of inflammation.

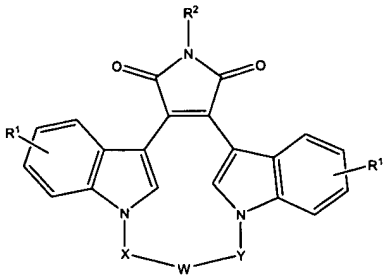
Paragraph 4 of Ito is equally devoid of any teaching related to inflammation. Paragraph 4 states that tofisopam has neither surface nor infiltrative anesthetic activity and instead, acts as a surface irritant.

In summary, none of Ito's paragraphs 1-5 are directed to the anti-inflammatory properties of tofisopam, nor would a person of ordinary skill in the art understand Ito to disclose as much. Rather, Ito provides a listing of activities, none of which have any evident or known relationship to inflammation. Thus, regardless of the dosages disclosed in Ito, a person of ordinary skill in the art would not have had any motivation to apply these dosages for treating an individual afflicted with an inflammatory disorder of epithelial tissue.

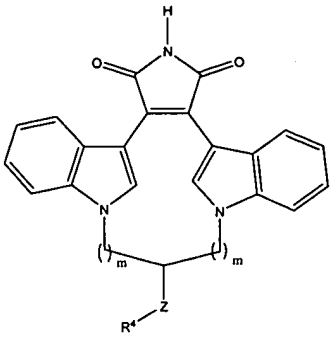
What is more, independent claim 1 now recites the (*R*) enantiomers of the benzodiazepines set forth in pending claim 1, substantially free of the (*S*) enantiomers. Ito's disclosure is limited to a racemic mixture of tofiospam. There is nothing in Ito that teaches or suggests any therapeutic indication of the tofisopam (*R*) enantiomer, substantially free of its (*S*) enantiomer, let alone its use for treating an inflammatory disorder of epithelial tissue.

In view of these deficiencies, a person of ordinary skill in the art would not have had rationale to consider Ito in the context of the present invention, let alone combine Ito with Jirousek.

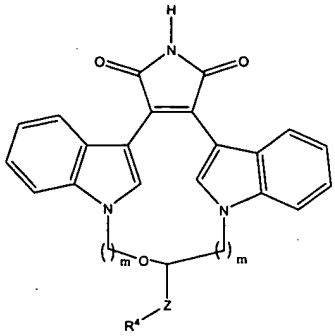
Even, however, had a person of ordinary skill in the art misconstrued Ito as the Examiner has, which he or she would not have, a person of ordinary skill in the art would still not have combined Ito and Jirousek. Specifically, Jirousek is directed to compounds having the following generic structures:



Formula I

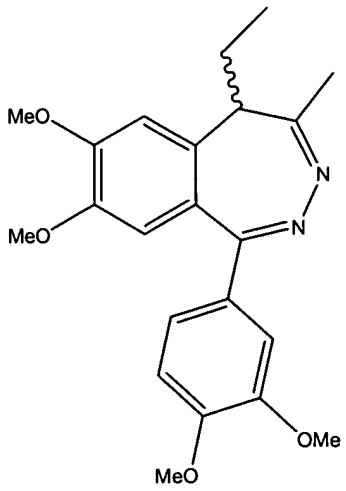


Formula II



Formula III

By way of distinction, tofisopam, has the following structure:



Racemic Tofisopam

Tofisopam has no indole functionality (let alone two indole units) and no 2,6-pyrrolidine dione, as in the Jirousek Formula I, II, and III compounds. What is more, there is nothing in Jirousek that teaches or suggests the interchangeability of compounds of Formulas I, II, or III with tofisopam, or benzodiazepines generally, as the words tofisopam, benzodiazepine, "BZ", valium, and diazepam do not appear in Jirousek at all.

Thus, in view of the substantial structural dissimilarities between Jirousek's compounds and tofisopam, as well as in view of the fact that Jirousek does not teach or suggest the interchangeability of its compounds for tofisopam (or benzodiazepines, generally), a person of

ordinary skill in the art would have no reason to believe that tofisopam would share any of the activity of the Jirousek compounds.

Even, however, had a person of ordinary skill in the art overlooked all of the above noted facts and combined Ito and Jirousek, which they would not have, the result would not be the presently claimed method. Instead, the result would be Ito's test methodology using any one of Jirousek's compounds. The result would not have been the invention as defined in claim 1.

In view of the above, the Applicants respectfully request that the Examiner withdraw the pending 35 U.S.C. §103(a) rejection as the Examiner has failed to set forth a *prima facie* case.

Conclusion

All claims remaining in the application are believed to be in condition for allowance. An early action toward that end is earnestly solicited.

Respectfully submitted,

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